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Use of busulfan in conditioning for allogeneic hematopoietic stem cell transplantation in adults: A survey by the Transplant Complications Working Party of the EBMT

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Abstract

A survey was carried out among EBMT centers about the use of busulfan for conditioning in allogeneic stem cell transplantation. Of 109 responding centers, 106 used busulfan for conditioning, 102 in conventional myeloablative doses, and 93 in reduced doses (RIC). The route of administration was mostly intravenous, but approximately ten per cent of the centers gave the drug orally. The number of doses in i.v. administration varied and was in myeloablative conditioning mostly one (50 centers) or four (43 centers) doses a day. Seventeen of the 106 centers used pharmacokinetics for dose adjustment in myeloablative conditioning, 9 in RIC. The details of pharmacokinetic monitoring varied markedly. Three quarters of the centers reported adjusting the dose based on obesity in myeloablative conditioning and about 60 % in RIC. The most common method for dose calculation was ideal body weight + 0.25 x (actual body weight – ideal body weight). In conclusion, the present survey showed marked heterogeneity in the current practices of busulfan administration for conditioning. The impact of the heterogeneity is not well known. Due to this and the scarcity of support from controlled clinical studies, no clear guidelines can be presented, but some prevailing policies to be recommended were identified.

Introduction

Busulfan-based conditioning in various combinations is widely used in allogeneic hematopoietic stem cell transplantation (HSCT). Busulfan was initially given orally in myeloablative doses, and for practical reasons typically in four daily doses on four consecutive days (1). Erratic absorption from the gut and thereby variable bioavailability resulted in deviations from the target exposure to the drug, causing sometimes undue organ toxicity. Therefore many centers began to adjust the doses based on pharmacokinetic (PK) measurements. With the introduction of an intravenous formulation, options for the administration increased. Intravenous administration was easier in practice, allowed more precise dosing and has widely replaced oral administration, although a minority of centers continue to use the oral route. The role of PK measurements, therapeutic drug monitoring (TDM), remains unclear particularly in i.v. administration (2). The practice of busulfan administration for conditioning at transplant centers is evidently heterogeneous, and details in which the policies of centers are likely to differ include the route of administration, number of daily doses, use of PK measurements, and adjustment of doses in obese patients. The possible impact of such differences on the outcome is unknown. The Transplant Complications Working Party of the European Society for Blood and Marrow Transplantation (EBMT) has carried out a survey among EBMT centers about their practice in the use of busulfan for conditioning in allogeneic HSCT in adults, with the aim of using the obtained information as support for potential recommendations toward standardization.

Methods

All allogeneic transplant centers reporting to the EBMT and treating adult patients were invited to participate in the survey. The questionnaire included 47 questions about the indications for busulfan conditioning, doses used, routes of administration, days of administration, number of daily doses, use of pharmacokinetics, adjustment of doses based on obesity, and preparations used (Supplementary material, Table 1). The survey was carried out from February to May 2017. Two reminders were sent to centers that had not responded. The survey was strictly anonymous, the information of the reporting center and person was only known to the data center but not to the investigators. Associations between center characteristics and busulfan use policy were tested with Fisher´s exact test. The studied parameters were transplant program size (50 or more vs. fewer allogeneic transplantations according to EBMT 2015 annual survey) (3), center experience (25 years or more vs. less), JACIE accreditation status, and gross national income per capita (GNI) of the country (www.Worldbank.com).

The intensity of conditioning, myeloablative (MAC) or reduced intensity (RIC), was registered as reported by the center. In some instances more than one alternative applied, and some questions in the questionnaire were not answered, leading to uneven sums.

The data were analyzed at the EBMT data center in Leiden, the Netherlands.

Results

One hundred and nine centers, 28% of all EBMT centers performing allogeneic transplantations to adult patients, participated and sent their report. Of these centers 106 used busulfan for conditioning, 102 in conventional myeloablative doses, and 93 in reduced doses. The distribution by country of the participating centers using busulfan conditioning is shown in Table 1. The diseases for which the transplantations were carried out are shown in Table 2.

The route of busulfan administration was mostly intravenous, but approximately ten per cent of the centers gave the drug orally (Fig. 1A). The characteristics of the centers using oral or i.v. administration did not differ in transplant program size, center experience, JACIE accreditation status, or GNI of the country.

Ninety-three centers determined the busulfan dose based on weight, seven centers based on body surface area.

Myeloablative oral doses, 16 mg/kg, were always given on four days, on each day four doses of 1 mg/kg, subject to dose modification in case TDM was used. In i.v. administration, the myeloablative total dose was most commonly approximately 12.8 mg/kg (69 centers). Other doses called myeloablative were given at 27 centers. When the dose was calculated based on body surface area, the total dose was 520 mg/m^2. Myeloablative i.v. doses were always administered in four days. The number of daily doses was mostly one (50 centers) or four (43 centers) (Fig. 1B).

In RIC transplantations, the most common policy was to reduce the number of days from that used in i.v. MAC, whereas the daily dose and the administration schedule

commonly remained the same. Sixty-five per cent of the centers reported giving busulfan on two days in RIC. The number of daily i.v. busulfan doses in RIC transplantations was most commonly one (40 centers) or four (28 centers) (Fig. 1B).

Overall, 17 of the 106 centers used PK measurements for busulfan dose adjustment in MAC, including 9 using such measurements also in RIC. The intensity of the conditioning did not significantly affect the proportion of centers using TDM (Fig. 1C). There was no significant difference between centers giving oral or intravenous busulfan in the use of pharmacokinetics for dose adjustment (Fig. 1D). The use of PK measurements was not significantly associated with transplant program size, center experience, JACIE accreditation status, or GNI of the country.

The PK measurements were carried out after the first dose in 12 centers while four centers allowed variability in timing; no data was received from one center. One center used a test dose 1-2 weeks prior to conditioning. The sampling for TDM depended on the number of daily doses and included at least 3 samples to cover the concentration-time curve, but the timing of sampling varied greatly, all centers having their own schedule. Busulfan concentration was measured with liquid chromatography coupled with mass spectrometry in 8 centers, and with liquid chromatography based on other detection methods in 5 centers. This information was lacking from 4 centers.The parameter used for dose adjustment was based on the area under the curve (AUC). The specific AUC-based parameters varied between centers, and no two target AUCs were reported identically. However, the estimate of the reported target ranges, translated to the total AUC after a single dose, was from less than 900 to 1500 µmol/l x min, corresponding to a cumulative AUC of the four-day treatment of about 60 to 100 mg/l

x h, i.e. the reported target values were similar to previous reports and recommendations (2). The model for AUC calculation was one-compartment model (n=4), noncompartmental analysis (n=3) or Bayesian modeling (n=2); this information was lacking from 8 centers. Four centers reported receiving the results of PK measurements on the day of the sampling, 10 centers on the next day, and one center on the third day.

Eight centers reported alternatives in the procedure of busulfan administration or target AUC depending on the disease, other components of the conditioning, or study protocols.

Approximately three quarters of the centers reported to adjust the busulfan dose based on obesity in MAC and about 60 % in RIC (Table 3). The definition of obesity and the way the dose was adjusted varied. The most common method for dose calculation was to use AIBW-25, ideal body weight + 0.25 x (actual body weight – ideal body weight) (4).

Discussion

The present survey showed a marked heterogeneity among allogeneic transplant centers in the details of their current use of busulfan for pre-transplant conditioning in allogeneic transplantations in adults. This is likely to be due to the limited evidence available to support any given practices and limitations in facilities for TDM.

The Practice Guidelines Committee of the American Society for Blood and Marrow Transplantation (ASBMT) recently published a report on their effort to develop an evidence-based review about personalizing busulfan-based conditioning (2). They

found that the published literature was too heterogeneous and lacked adequately powered and sufficiently controlled studies for their aim to be feasible. However, they presented a document addressing topics of practical relevance in busulfan conditioning. In line with the observations of the Practice Guidelines Committee, the findings of the present survey about the heterogeneity of the current practices reflect the lack of standard procedures in busulfan-based conditioning.

As expected, busulfan was used in conventional or reduced doses in a large majority of centers and for a wide spectrum of disorders. With the 28 % response rate there may be some reporting bias, but the presented findings are likely to reflect in a satisfactory way the general state of the use of busulfan conditioning at EBMT centers.

Busulfan was administered intravenously in close to 90 per cent of the centers. The obvious advantages of the i.v. route are easy administration, avoiding problems caused by gastrointestinal irritation, more precise dosing avoiding the variable absorption from the gut and thereby variable bioavailability, and avoiding first-pass metabolism in the liver. A reason for using the oral route is lower cost. There were no significant differences in the characteristics of the centers giving the drug orally and those using the i.v. route.

Oral busulfan is administered in four daily doses for practical reasons, difficulties with swallowing large numbers of tablets and gastrointestinal irritation. When i.v. busulfan became available, the traditional schedule was initially transferred to i.v. administration. However, evidence has since been presented that the daily dose can be given in one dose without untoward consequences (5,6). The pharmacokinetics are similar with one and four daily doses, but as obvious, the peak concentration of

busulfan is higher and the trough concentration lower with single daily doses (6). Generally no significant differences in adverse effects related to this difference in peak concentrations have been observed, and there is to our knowledge no evidence to suggest a difference in clinical efficacy. There is an obvious practical advantage in giving one daily infusion instead of four. Despite this, close to half of the centers reported dividing the daily i.v. busulfan dose in four doses.

The policy with busulfan dose adjustment based on PK measurements should be based on documentation of clinical benefits, reducing complications or improving efficacy. Several reports have shown an association between high exposure to busulfan and increased toxicity (7-14), and low busulfan exposure has been shown to correlate with more frequent graft rejection (9, 14-16). Several studies have indicated an association between busulfan exposure and transplant-related mortality, or event-free or overall survival (14, 17-20). As to specific diseases, busulfan exposures have been shown to associate with relapse rate in previously untreated CML, higher exposures leading to lower relapse rate (21). In a randomized prospective trial in AML and MDS, pharmacokinetically guided busulfan delivery led to lower relapse risk and treatment-related mortality as well as to higher overall and event-free survival compared to fixed dose administration (22). However, the documentation from controlled clinical trials of concrete clinical benefits of busulfan TDM is still limited, and there is no general consensus about the utility of pharmacokinetics for busulfan dose adjustment (2). It is also to be noted that the impact of busulfan TDM may be different in different conditioning regimens. Overall, there are no widely followed guidelines about the use of PK measurements in this context. The report from the ASBMT Practice Guidelines Committee (2) concludes that busulfan TDM is currently considered unnecessary in RIC

231 transplantations. There was no conclusive statement of a recommendation to monitor
232 busulfan concentrations in transplantations with conventional busulfan doses. Another
233 report from the same organization states that all regimens with a more than 12 mg/kg
234 oral dose equivalent are recommended to have PK targeting as appropriate for the
235 disease (23).

236 One of the centers participating in the present survey used a test dose before the
237 conditioning to calculate the busulfan doses based on pharmacokinetics. This approach
238 has recently been applied by several groups (11, 22, 24-28), but the ASBMT document
239 did not recommend the use of a test dose (2).

240 The present survey shows that busulfan TDM is used in only a minority, approximately
241 15 % of the EBMT centers. Among patients reported to the CIBMTR (Center for
242 International Bone and Marrow Transplant Research) in 2008, more than 60 % of those
243 who received oral busulfan and 50 % of those receiving i.v. busulfan had PK data (29).
244 Oral administration, with potentially erratic absorption from the gut, could be expected
245 to be a particular reason to use TDM, but in the present study there was no significant
246 difference in the use of busulfan measurements between centers using oral or i.v.
247 administration. Similarly, conventional busulfan doses could have been expected to be
248 a stronger indication to TDM compared to reduced doses, but busulfan PK
249 measurements were used approximately equally often in connection with conventional
250 and RIC doses. Reasons for this situation may include uncertainty about concrete clinical
251 benefit, but possibly also limited availability of laboratory service for busulfan
252 measurements, AUC calculations and dose recommendations may be contributing

253 factors in the present state. The center characteristics of those using or not using PK
254 measurements did not differ significantly.

255 There was marked variability in the practical details of the TDM, in the timing of
256 measurements, units used, and the method to calculate AUC; no two centers reported
257 an identical TDM protocol. However, the estimate of the reported target ranges,
258 translated to the total AUC after a single dose, indicated that the target values were
259 similar to previous reports and recommendations (2). These results seem to reflect the
260 current situation that there are recommendations for the concentration target for
261 busulfan, but consensus guidelines concerning the method used for AUC estimation are
262 lacking.

263 Approximately three quarters of the centers reported adjusting myeloablative busulfan
264 doses based on obesity, whereas about 25 per cent did not make such adjustments.
265 There was marked variation in how the adjustments were determined, but the most
266 common policy was based on AIBW-25, in line with the ASBMT recommendations (23).
267 In the survey by the EBMT Acute Leukemia Working Party of chemotherapy dose
268 adjustment for obese patients in HSCT (30), 80.5 per cent of the centers adjusted the
269 doses. Sixty-two percent used body mass index as the parameter for defining obesity,
270 and the most common methods for dose calculation were based on actual body weight
271 or AIBW-25, each in approximately one third of the centers. There is to our knowledge
272 no solid clinical evidence of the benefits of dose adjustment based on obesity, but as
273 the drug exposure may become markedly different in grossly obese patients depending
274 on whether adjustments are or are not made (30), a study focusing on this issue would
275 be desirable.

Constitutional genetic polymorphisms might be a factor in individualizing busulfan doses. Particularly associations between the polymorphisms of genes associated with glutathione S-transferases and the clinical outcomes after busulfan conditioning have been a topic of discussion (2). However, the available documentation of the impact of such associations has been regarded as insufficient for a recommendation to use genetic polymorphism for personalizing busulfan doses in routine clinical practice (2).

The present survey shows marked heterogeneity in the current practices of busulfan administration for conditioning. Due to this and the scarcity of support from controlled clinical studies, no clear guidelines based on solid documentation or dominating practice can be presented. However, some prevailing policies can be identified and commented on:

- A large majority of centers give busulfan i.v., but a significant minority still use the oral route. Low costs favor oral administration, but otherwise there are both practical and theoretical advantages for i.v. administration.
- I.v. busulfan can be given in one daily dose, but almost half of the centers divide the daily dose in four infusions. There is no evidence to suggest any advantage to the divided doses, and therefore a single daily dose seems to be the policy to be recommended.
- PK-based dose adjustment is only used in a small minority of centers, even in transplantations with myeloablative busulfan doses. Although busulfan TDM seems logical, the evidence for clinical benefit especially in i.v. administration is limited. Several studies from recent years have presented data to support the use of pharmacokinetics for dose adjustment, but at this time it does not seem possible to

present well-founded recommendations for the use of busulfan TDM, particularly not in i.v. administration.

- There has been a lack of consistency in AUC based dose adjustment practices, particularly regarding the AUC based target parameter used, demonstrating a need for development of best-practice guidelines.
- The policy of dose adjustment for obesity is heterogeneous. Busulfan TDM would in principle be logical in obese patients, but documentation of its usefulness in this situation is obviously lacking.

In conclusion, the clinical impact of the observed heterogeneity in the application of test strategies, the use of PK guided dose measurements, or adjustments for body weight remain poorly defined. The effects of such variability on outcomes such as toxicity and relapse would ideally be evaluated in randomized trials.

Competing interests

The authors declare no competing financial interests.

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439 **Legend to Figure**

440

441 Figure 1. Administration of busulfan in myeloablative (MAC) and reduced intensity
442 (RIC) conditioning; numbers of centers. A: route of administration; B: number of
443 daily doses; C: therapeutic drug monitoring (TDM) used; D: TDM used in relation
444 to route of administration.

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